Cancer Chemother Pharmacol (1992) 30: 365–369

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of liposome-entrapped *cis*-bis-neodecanoato-*trans*-*R*,*R*-1,2-diaminocyclohexane platinum(II) and cisplatin given i.v. and i.p. in the rat*

Kiumars Vadiei[3, 4], Zahid H. Siddik[2], Abdul R. Khokhar[2], Salam Al-Baker[2], Federico Sampedro[3], and Roman Perez-Soler[1]

[1] Section of Head, Neck, and Thoracic Medical Oncology, [2] Section of Pharmacology, and [3] Section of Immunobiology and Drug Carriers, Department of Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, and [4] Clinical Research and Development, Wyeth-Ayerst Research, Radnor, PA 19087, USA

Received 26 November 1991/Accepted 3 March 1992

Summary. The pharmacokinetics of liposome-entrapped *cis*-bis-neodecanoato-*trans*-*R*,*R*-1,2-diaminocyclohexane platinum(II) (L-NDDP) and cisplatin (CDDP) were studied after i.v. and i.p. administration of an equimolar dose (11 and 5 mg/kg for L-NDDP and CDDP, respectively) in the rat. The systemic absorption following i.p. administration was faster in rats receiving CDDP than in those receiving L-NDDP. Peak serum platinum (Pt) levels were observed at 30 min and 12 h after the i.p. administration of CDDP and L-NDDP, respectively. Administration by the i.v. route did not significantly alter the serum Pt levels for either compound. However, serum Pt levels were 2–3 times greater in animals treated with L-NDDP than in those treated with CDDP. The estimated pharmacokinetic parameters for each drug were independent of the route of administration, except for the clearance (*Cl*) of CDDP, which increased 2-fold following i.p. administration. In addition, significant differences in pharmacokinetic parameters were observed between drug-treatment groups that were independent of the route of administration: the serum Pt area under the concentration-time curve (AUC) was higher and the volume of distribution at steady state (Vd_{ss}) was lower in rats receiving L-NDDP. Pt levels measured at 6 h in the peritoneal fluid, peritoneal tissue, and intestine of rats receiving i.p. L-NDDP were higher than those observed in rats receiving either i.v. L-NDDP or CDDP by either route. Pt levels measured in the liver and spleen of rats receiving L-NDDP were independent of the route of administration and were significantly higher than those determined in rats treated with CDDP. In contrast, kidney Pt levels were lower in rats receiving L-NDDP than in rats receiving CDDP by either route. These results suggest that the prolongation of the mean retention time of L-NDDP in the peritoneum achieved after i.p. administration without compromising the systemic distribution of the drug may result in a significant enhancement of the therapeutic efficacy of L-NDDP against malignancies confined to the peritoneal cavity as compared with that of i.p. CDDP.

* This study was supported in part by NIH grants CA-45423 and CA-41581

Offprint requests to: R. Perez-Soler, Department of Medical Oncology, Box 80, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas 77030, USA

Introduction

Cisplatin (CDDP) is one of the most effective agents for the treatment of lung, head and neck, testicular, ovarian, bladder, and bone cancer [4, 8]. However, its use is limited by acute dose-related renal toxicity and chronic neurotoxicity [16]. Different strategies have been explored to enhance the therapeutic index of CDDP. Efforts to synthesize superior analogs have resulted in the development of carboplatin, which has an improved therapeutic index due to its lower nephrotoxicity [7]. However, the spectrum of antitumor activity of carboplatin has not been broadened by its reduced nephrotoxicity and safer administration. Modifications of the administration schedule (i.e., continuous infusion) and prehydration with mannitol have also been shown to reduce the gastrointestinal side effects and nephrotoxicity of CDDP, respectively [1].

L-NDDP is a lipophilic platinum (Pt) complex developed in our laboratory using a liposomal carrier for its parenteral administration [11]. In preclinical studies, L-NDDP has not been nephrotoxic in mice and dogs [6] and has shown significantly more activity than CDDP in vivo against both murine leukemias that are resistant to CDDP and liver metastases of M5076 reticulosarcoma [10]. In pharmacology studies in rabbits, blood and organ levels of elemental Pt have increased severalfold in animals treated with L-NDDP as compared with animals treated with an equimolar dose of CDDP [6]. A phase I study on L-NDDP has recently been conducted at M. D. Anderson Cancer Center [13].

Recently, several investigators have obtained an improved therapeutic effect using i.p. administration of CDDP for the treatment of small-volume ovarian cancer, a disease that tends to disseminate within the peritoneal cav-

ity [3, 15]. This approach does not appear to be as successful in bulky disease due to the relative inability of CDDP to penetrate the tumor tissue.

Because of the large size of the liposomes in the L-NDDP formulation (1–5 μm) [6], it is very unlikely that they reach the blood circulation intact after i.p. administration. Thus, absorption of NDDP into the blood requires the destruction of the liposomes or the fusion and transfer of their content into the mesothelial cells, tumor cells, and capillary endothelial cells that are in direct contact with the cavity space. Therefore, after i.p. administration of L-NDDP, it would be reasonable to expect a slow absorption of the drug into the blood circulation and, as a result, a markedly prolonged exposure of the structures in direct contact with the peritoneal cavity to L-NDDP. The combination of both factors may result in an improved local antitumor effect.

To test this hypothesis, we studied the pharmacokinetics and tissue distribution of L-NDDP and CDDP after their i.v. and i.p. administration to rats. The results demonstrate that following its i.p. injection, L-NDDP is retained in the peritoneal cavity longer than CDDP, resulting in increased drug levels in the peritoneal tissue, and does not significantly alter the overall systemic exposure to the drug.

Materials and methods

Drugs. Cisplatin (Bristol-Labs, Syracuse, N. J.) was reconstituted in sterile water at a final concentration of 1 mg/ml. L-NDDP was prepared as described elsewhere [8, 11]. Briefly, dimyristol-phosphotidylcholine (DMPC) and dimyristol-phosphatidyglycerol (DMPG) (Avanti Polar Lipids, Pelham, Ala.) were mixed with NDDP (DMPC : DMPG : NDDP weight ratio, 10.5 : 4.5 : 1) and dissolved in chloroform. The solvent was evaporated in a rotavapor and the lipid film containing the drug was redissolved in t-butanol. The solution was frozen in a dry ice/acetone bath and lyophilized for 24 h. The lyophilizate was reconstituted in sterile water to a final concentration of 2 mg/ml by mild manual shaking.

Animals. Adult male Sprague-Dawley rats (250–350 g; Charles River Breeders, Wilmington, MA) were given standard rat chow and water ad libitum for 1 week prior to experimentation. Animals were maintained on a 12-h light-dark cycle in an animal facility under constant humidity and temperature. Experimental procedures were approved by the Animal Care Committee of The University of Texas M. D. Anderson Cancer Center and were carried out in accordance with the guidelines established by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

Study design: pharmacokinetics study. Rats were placed under anesthesia by the administration of i.p. pentobarbital (50 mg/kg) and were divided into four groups as follows: group 1, i.v. L-NDDP (11 mg/kg, $n = 5$); group 2, i.p. L-NDDP (11 mg/kg, $n = 4$); group 3, i.v. CDDP (5 mg/kg, $n = 7$); and group 4, i.p. CDDP (5 mg/kg, $n = 3$). For i.v. administration, drugs were injected into the penile vein, and the injection volume was 5.5 ml/kg for both i.v. and i.p. injection. The L-NDDP and CDDP doses used were equimolar. Serial blood samples were obtained by tail bleeding at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, and 48 h postinjection. Blood samples collected after 2 h were obtained from rats under light metafane anesthesia. Following the final blood sampling, the animals were humanely killed in a CO_2 chamber. Blood samples were first allowed to clot and then centrifuged to obtain serum. Serum samples were stored at –20° C until their analysis for Pt levels (within 2 weeks).

Study design: tissue distribution. Rats were placed under anesthesia by the administration of i.p. pentobarbital (50 mg/kg) and were randomized into four groups as described above for the pharmacokinetics study ($n = 3$ rats in each group). At 6 h postinjection, rats were given 10 ml saline by i.p. injection and the abdomen was gently shaken for 2 min. The abdomen was then opened and a 3-ml aliquot of the peritoneal fluid was removed. A 1-ml blood sample as well as liver, spleen, kidney, intestine, and peritoneal tissue (fascia) samples were obtained. The serum was harvested from the clotted blood, and tissue samples were blot-dried. All samples were frozen at –20° C until their analysis for Pt levels (within 2 weeks).

Sample analysis. Serum samples were diluted (by 50% or more if necessary) with 0.1 *N* HCl, briefly vortexed, and analyzed for elemental Pt by flameless atomic absorption spectrophotometry (FAAS) [17]. Tissue aliquots (200 mg) were placed in a drug-free scintillation vial containing 0.5 ml hyamine hydroxide (Sigma, St. Louis, Mo.). Tissue samples were incubated for 5 h at 55° C to facilitate digestion of the tissues. Subsequently, each vial was vortexed for 3 min, and 4 vol. 0.3 *N* HCl was added to each sample. Elemental Pt was measured by FAAS [17].

Data analysis. Pt concentrations were determined from a standard curve obtained by the standard-additions method as previously described by Siddik et al. [17]. A new standard curve was constructed for each set of serum samples obtained from individual animals to minimize assay variability. Pharmacokinetic analysis was performed using noncompartmental methods [2]. The elimination rate constant (K) was determined by regression analysis of the terminal points. The area under the Pt concentration-time curve (AUC) was estimated using the trapezoidal rule and extrapolated to infinity by the addition of c_t/K, where c_t represents the final concentration at 48 h. The total clearance was calculated as the dose divided by the AUC. The volume of distribution at steady state was determined by the following equation:

$$Vd_{ss} = \text{Dose} \times \text{AUMC}/\text{AUC}^2,$$

where *AUMC* represents the area under the first-moment Pt concentration-time curve. The maximal Pt peak concentration (c_{max}) and peak time (t_{max}) were obtained by extrapolation for the i.v. dose and estimated visually for the i.p. dose from the concentration-time profile.

Statistical analysis. The differences observed in the pharmacokinetic parameters and tissue Pt concentrations within and between treatment groups were analyzed for statistical significance using Student's *t*-test and analysis of variance. A difference was considered to be significant when the probability of chance explaining the results was reduced to less than 5% ($P < 0.05$).

Results

Figures 1 and 2 show the concentration-time profiles obtained for Pt after i.v. and i.p. administration of equimolar doses of CDDP and L-NDDP. In the case of CDDP, the route of administration did not significantly change the concentration-time profile of Pt (Fig. 1). The peak absorption of CDDP into the circulation after i.p. administration occurred within 30 min. In contrast, i.p. administration of L-NDDP resulted in a delayed absorption of the drug into the circulation, peak serum Pt levels being detected at aproximately 12 h postinjection (Fig. 2). Figures 3 and 4 show the serum concentration-time profile obtained for Pt in animals treated with equimolar doses of CDDP and L-NDDP according to the route of administration. When both agents were injected i.v. (Fig. 3), the Pt concentration-time curves were similar, although Pt levels were uniformly elevated in the animals treated with L-NDDP. After i.p. administration (Fig. 4), peak serum Pt levels were reached at approximately 12 h after the injection of

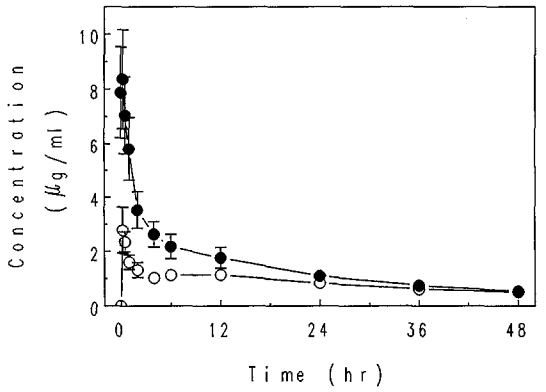

Fig. 1. Concentration-time profile of Pt in serum following a single i.v. (●) and i.p. (○) dose of CDDP in the rat. Data represent mean values ± SD

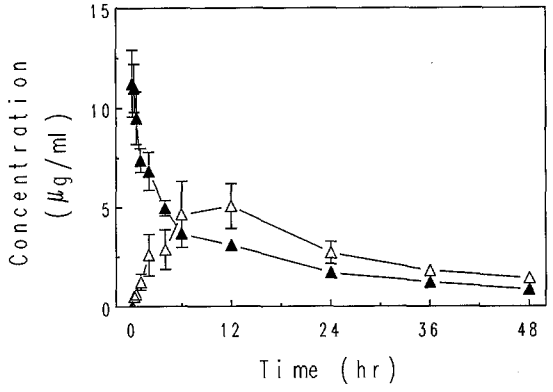

Fig. 2. Concentration-time profile of Pt in serum following a single i.v. (▲) and i.p. (△) dose of L-NDDP in the rat. Data represent mean values ± SD

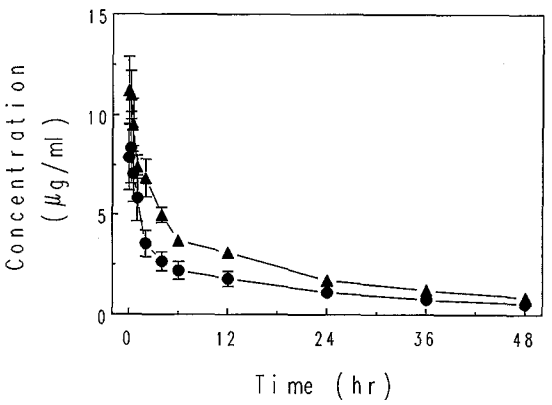

Fig. 3. Concentration-time profile of Pt in serum following a single i.v. dose of L-NDDP (▲) and CDDP (●) in the rat. Data represent mean values ± SD

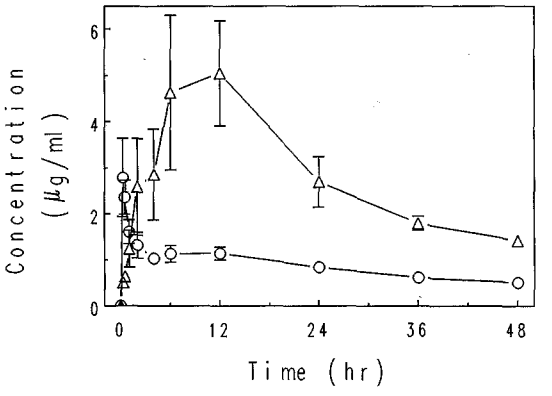

Fig. 4. Concentration-time profile of Pt in serum following a single i.p. dose of L-NDDP (△) and CDDP (○) in the rat. Data represent mean values ± SD

L-NDDP, whereas they were detected within 30 min of CDDP administration. Peak serum Pt levels determined after i.p. injection of L-NDDP were 2-fold those measured following i.p. treatment with CDDP (5.1±2.3 vs 2.9±1.4 μg/ml, P <0.05).

Table 1 shows the pharmacokinetic parameters estimated for CDDP and L-NDDP after i.p. and i.v. administration of equimolar doses of these agents. When the results were independently analyzed for each drug, no significant change in the pharmacokinetic parameters was observed as a result of changing the route of administration from i.v. to i.p. except in the case of CDDP, whose Cl increased about 2-fold following i.p. injection (0.04±0.01 vs 0.02±0.01 l h^{-1} kg^{-1}, P <0.05).

The AUC value obtained for i.v. L-NDDP was about 30% greater than that found for i.v. CDDP (197.3±22.5 vs 141.3±22.9 μg h ml^{-1}, P <0.05). Following i.p. injection of the drugs, this difference increased to a more than 2-fold discrepancy as a result of an increase in the AUC value for L-NDDP and a decrease in the AUC value for CDDP (231.7±50.9 vs 103.3±30.8 μg h ml^{-1}, P <0.05). The Vd_{ss} value obtained for CDDP following i.p. administration was 3-fold that found for either i.p. or i.v. L-NDDP. Although the difference did not reach statistical significance, the $t_{1/2}$ value found for L-NDDP was lower than that observed for CDDP, regardless of the route of administration.

Table 2 shows the Pt levels measured in peritoneal fluid and different organs at 6 h after i.p. and i.v. administration of equimolar doses of CDDP and L-NDDP to rats. When the results were analyzed according to the mode of treatment, i.p. administration was found to increase the Pt levels in both the peritoneal tissue and the intestine by a factor of 2–3 for both CDDP (4.9±1.8 vs 1.9±0.5 μg/g, P <0.05) and L-NDDP (9.3±5.4 vs 3.6±0.9 μg/g, P <0.05). Following i.p. administration, a 4- to 5-fold increase in the Pt levels in peritoneal fluid was noted only in rats receiving L-NDDP, whereas no change was observed in animals treated with CDDP. Other Pt tissue levels were not altered by i.p. administration. When tissue levels of Pt observed in animals receiving i.p. L-NDDP were compared with those found in animals treated i.p. with CDDP, the levels detected in the peritoneal fluid (362±193 vs 7±2 ng/ml, P <0.05), peritoneal tissue (9.3±5.4 vs 4.9±1.8 μg/g, P <0.05), intestine (10.0±5.1 vs 4.7±1.9 μg/g, P <0.05), liver (13.9±4.1 vs 4.1±2.3 μg/g, P <0.05), and the spleen (13.9±4.4 vs 2.1±1.6 μg/g, P <0.05) of rats receiving L-NDDP were 60-, 2-, 2-, 3-, and 6-fold those measured in animals treated with CDDP, whereas the Pt levels detected in the kidney of

Table 1. Pharmacokinetic parameters of CDDP and L-NDDP after the administration of single i. v. or i. p. doses to rats.

Parameter	Treatment groups			
	CDDP		L-NDDP	
	i. v.	i. p.	i. v.	i. p.
$t_{1/2}$ (h)	71.4 ±35.7	69.3 ±23.2	45.8 ± 6.2	46.3 ±11.8
AUC (μg h ml^{-1})	141.3 ±22.9	103.3 ±30.8	197.3 ±22.5*1, *2	231.7 ±50.9*1, *2
Cl (l h^{-1} kg^{-1})	0.023 ± 0.005	0.041 ± 0.010*1, *3, *4	0.018 ± 0.005	0.013 ± 0.005
Vd_{ss} (l/kg)	1.9 ± 1.5	3.3 ± 0.19*3, *4	0.69 ± 0.14	0.89 ± 0.38
c_{max} (μg/ml)	7.9 ± 4.4	2.9 ± 1.4	11.2 ± 3.7	5.1 ± 2.3*3
t_{max} (h)	0	0.5	0	12.0

Data represent mean values ± SD
*1 P <0.05 vs i. v. CDDP; *2 P <0.05 vs i. p. CDDP; *3 P <0.05 vs i. v. L-NDDP; *4 P <0.05 vs i. p. L-NDDP

Table 2. Pt levels found in the peritoneal fluid and tissues of rats treated with a single i. v. or i. p. dose of CDDP or L-NDDP at 6 h after drug administration.

Samples	Treatment groups			
	CDDP		L-NDDP	
	i. p.	i. v.	i. p.	i. v.
Peritoneal fluid (ng/ml)	7 ±2	6 ± 1	363 ±193*1-*3	25 ±12
Peritoneal tissue (μg/g)	4.9±1.8	1.9± 0.5	9.3± 5.4*1-*3	3.6± 0.9
Intestine (μg/g)	4.7±1.9	2.7± 1.2	10.0± 5.1*1-*3	2.5± 2.4
Liver (μg/g)	4.1±2.3	6.5± 3.1	15.9± 4.1*1, *2	16.8± 1.9*1, *2
Spleen (μg/g)	2.1±1.6	3.3± 1.6	13.9± 4.4*1, *2	14.6± 2.9*1, *2
Kidney (μg/g)	20.7±9.9	19.9±10.8	8.0± 1.8	8.6± 3.2

Data represent mean values ± SD
*1 P <0.05 vs i. v. CDDP; 2 P <0.05 vs i. p. CDDP; *3 P <0.05 vs i. v. L-NDDP; *4 P <0.05 vs i. p. L-NDDP

rats receiving CDDP were about 2- to 3-fold those measured in animals treated with L-NDDP (8.0±1.8 vs 20.7±9.9 μg/g, NS).

Discussion

Our results indicate that the pharmacokinetics and organ distribution of L-NDDP and CDDP after i. p. administration are significantly different. The absorption of L-NDDP into the circulation from the peritoneal cavity is much slower than that of CDDP, peak Pt levels being reached at 12 h after i. p. administration of the former and within 30 min of i. p. administration of the latter. Additional differences between the pharmacokinetics of the two drugs were observed independently of the route of administration; serum Pt AUC and Vd_{ss} values were significantly elevated and decreased, respectively, in rats treated with L-NDDP as compared with those receiving CDDP. Finally, in spite of the slow absorption of L-NDDP from the peritoneal cavity into the systemic circulation, the pharmacokinetic parameters of L-NDDP were not significantly altered by i. p. administration of the drug.

A phase I clinical study on L-NDDP has been conducted at M. D. Anderson Cancer Center [13]. The dose-limiting toxicity of L-NDDP was myelosuppression, and no evidence of nephrotoxicity was observed. Other toxicities encountered at the maximum tolerated dose were mild and consisted of nausea, vomiting, diarrhea, fever, transient elevations of liver enzymes, and malaise. The Pt AUC value was the only pharmacokinetic parameter that correlated somewhat with toxicity in the phase I study of L-NDDP in humans. No significant difference in AUC values was observed between i. p. and i. v. L-NDDP-treated rats. Assuming that this finding can be extrapolated to humans, systemic distribution of L-NDDP should not be affected by the route of administration. Therefore, the systemic toxicity and antitumor activity of L-NDDP should be approximately the same after i. v. or i. p. administration. The Pt AUC value tended to decrease following i. p. administration of CDDP. This might compromise the systemic antitumor activity of the drug but might also decrease its systemic toxicity. However, kidney Pt levels measured at 6 h after CDDP treatment were independent of the route of administration.

Large multilamellar vesicles (1–5 μm) similar to the liposomes prepared and used in the present study have demonstrated extensive and selective distribution and accumulation in organs of the reticuloendothelial system, including the liver, spleen, and bone marrow [9]. In agreement with previous studies [10], Pt concentrations were significantly higher in the liver and spleen of rats receiving L-NDDP than in those treated with CDDP. Renal Pt concentrations increased 2-fold in rats treated with CDDP as compared with those receiving L-NDDP, regardless of the route of administration. Although renal function was not

measured, the data not only suggest an increased advantage of L-NDDP over CDDP as a result of reduced accumulation of Pt in the kidney as observed previously but also indicate that the lack of renal toxic effects of L-NDDP may not be compromised by changing the route of administration from i.v. to i.p.

The tissue distribution of L-NDDP appears to be independent of its route of administration. Since liposomes are most likely not absorbed intact from the peritoneal cavity into the systemic circulation, significant differences in tissue distribution would be expected unless the life span of the liposomes in the blood were quite short and significant drug leakage were to occur shortly after i.v. administration, in which case the tissue distribution after i.v. and i.p. administration of L-NDDP should be similar and should correspond to the distribution of free NDDP. Transfer of NDDP to serum lipoproteins shortly after its i.v. administration could explain these surprising findings and is currently being investigated.

The i.p. administration of L-NDDP as compared with CDDP resulted in a marked increase (60-fold) in the Pt levels measured in peritoneal fluid at 6 h posttreatment, as expected from the differences in the absorption of L-NDDP and CDDP from the peritoneal cavity. This finding, although limited to one time point, strongly suggests a marked pharmacological advantage for the targeting of peritoneal malignancies for treatment with i.p. L-NDDP as compared with i.p. CDDP due to the considerably prolonged exposure of the peritoneum to the former drug.

Our study also shows that CDDP is more effective than L-NDDP in diffusing through the normal peritoneal tissue and, as a result, in reaching the systemic circulation. However, the increased Pt concentration observed in the intestine and peritoneal tissue of rats after i.p. L-NDDP administration suggests an enhanced penetration of the drug into normal tissues close to the peritoneal surface. It is not yet known whether this may also apply to malignancies in contact with the cavity. A significant determinant of intracellular drug accumulation may be the lipophilicity of the compound. A study by Los and co-workers [5] has demonstrated that oxaliplatin, a Pt complex that is more lipophilic than CDDP, exhibits better transmembrane-diffusion characteristics and increased activity against peritoneal tumors following its i.p. administration to rats. We have previously reported that the cellular uptake of L-NDDP is 5- to 8-fold that of CDDP [17]. The mechanisms underlying the enhanced cellular uptake of L-NDDP have not been elucidated but are probably related to its high affinity for lipid membranes. It would therefore be reasonable to predict from the information currently available that the different mechanism of transmembrane transport of L-NDDP may result in an enhancement of its tumor penetration as compared with that of CDDP.

In summary, the current study indicates a potential pharmacological advantage for the i.p. administration of L-NDDP as compared with CDDP due to the markedly increased retention time of the former agent in the peritoneal cavity. These results, combined with the previously reported lack of cross-resistance of L-NDDP with CDDP, may justify the study of i.p. L-NDDP in patients with ovarian carcinoma refractory to CDDP.

References

1. Chary KK, Higby DJ, Henderson ES, Swinerton KD (1977) Phase I study of high dose *cis*-dichlorodiammineplatinum(II) with forced diuresis. Cancer Treat Rep 61: 367–370
2. Gibaldi M, Perrier D (1982) Pharmacokinetics, 2nd edn. Marcel Dekker, New York
3. Howell SB, Zimm S, Markman M, Abramson IS, Cleary S, Lucas WE, Weiss-Regis J (1987) Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. J Clin Oncol 5: 1607–1612
4. Loehrer PJ, Einhorn LH (1984) Cisplatin. Ann Intern Med 100: 704–713
5. Los G, Mutsaers PHA, Ruevekamp M, McVie JG (1990) The use of oxaliplatin versus cisplatin in intraperitoneal chemotherapy in cancers restricted to the peritoneal cavity in the rat. Cancer Lett 51: 109–117
6. Khokhar AR, Wright K, Siddik ZH, Perez-Soler R (1988) Organ distribution and tumor uptake of liposome entrapped *cis*-bis-neodecanoato-*trans-R,R*-1,2-diaminocyclohexane platinum(II) administered intravenously and into the proper hepatic artery. Cancer Chemother Pharmacol 22: 223–227
7. Paraplatin (carboplatin): Current status and future prospects (1985) In: Carter SK, Hellmann K (eds) Proceedings of the 3rd European conference on clinical oncology. Cancer Treat Rev 12 [Suppl A]: 1–152
8. Penta JS, Muggia FM, Salem PA (1983) Cisplatin in cancer therapy. Optimisation of treatment regimens and toxicity protection. In: Muggia FM (ed) Cancer chemotherapy. Martinus Nijhoff, The Hague, Netherlands, pp 149–169
9. Perez-Soler R, Lopez-Berestein G, Jahns M, Kasi LP, Cabanillas F, Jahns M, Glen H, Hersh EM, Haynie T (1985) Distribution of technetium 99m labels multilamellar liposomes in patients with Hodgkin's disease. J Nucl Med 26: 743–749
10. Perez-Soler R, Khokhar AR, Lopez-Berestein G (1987) Treatment and prophylaxis of experimental liver metastases of M5076 reticulosarcoma with *cis*-bis-neodecanoato-*trans-R,R*-1,2-diaminocyclohexane platinum(II) encapsulated in multilamellar vesicles. Cancer Res 47: 6462–6466
11. Perez-Soler R, Lopez-Berestein G, Khokhar AR (1988) Design and development of liposome-dependent antitumor agents. In: Lopez-Berestein G, Fidler I (eds) Liposomes in the treatment of infectious disease and cancer. (UCLA symposia on molecular and cellular biology, new series, vol 89) Alan Liss, New York, pp 59–69
12. Perez-Soler R, Yang LY, Drewinko B, Lautersztain J, Khokhar AR (1988) increased cytotoxicity and reversal of resistance to cisplatin with entrapped *cis*-bis-neodecanoato-*trans-R,R*-1,2-diaminocyclohexane platinum(II) in multilamellar lipid vesicles. Cancer Res 48: 4509–4512
13. Perez-Soler R, Lopez-Berestein G, Lautersztain J, Al-Baker A, Francic K, Macias-Kiger D, Raber MN, Khokhar AR (1990) Phase I clinical and pharmacological study of liposome-entrapped *cis*- bis-*trans*-neodecanoato-*R,R*-1,2-diaminocyclohexane platinum(II). Cancer Res 50: 4254–4259
14. Perez-Soler R, Siddik ZH, Vadiei K, Krakoff IH, Khokhar AR (1992) Pharmacological studies with new liposome-entrapped cisplatin derivatives. In: Howell SB (ed) Proceedings of the 6th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy. Plenum, New York (in press)
15. Pfeiffer P, Asmussen L, Kvist-Poulsen H, Bertelsen K (1989) Intraperitoneal chemotherapy: introduction of a new "single use" delivery system – a preliminary report. Gynecol Oncol 35: 47–49
16. Reed E, Kohn KW (1990) Platinum complexes. In: Chabner BA, Collins JM (eds) Cancer chemotherapy. Principles and practice. J. B. Lippincott, Philadelphia, pp 465–490
17. Siddik ZH, Boxall FE, Harrap KR (1987) Flameless atomic absorption spectrophotometric determination of platinum in tissue solubilized in hyamine hydroxide. Anal Biochem 163: 21–26